REVIEW PAPER

Impact of Clinical Pharmacokinetics on Neuroleptic Therapy in Patients with Schizophrenia*

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In memoriam
Dr. Theodore Van Putten

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This review covers some recent work on: 1. the effects of route of administration on the pharmacokinetics of fluphenazine and some of its metabolites; 2. the clinical pharmacokinetics of fluphenazine in acute patients medicated with oral fluphenazine; 3. the clinical pharmacokinetics of haloperidol in acute patients medicated with oral haloperidol; 4. the clinical pharmacokinetics of fluphenazine in the maintenance of individuals with chronic schizophrenia with fluphenazine decanoate; 5. a systematic dose reduction study in maintenance treatment refractory patients with oral haloperidol.

A study in which plasma levels of fluphenazine and fluphenazine sulfoxide were measured in a group of DSM-III-R patients with schizophrenia before and after switching from oral fluphenazine to depot fluphenazine, decanoate revealed much higher levels of fluphenzaine sulfoxide with oral medication compared with those found with depot fluphenazine. These data illustrate the effect of "first pass" metabolism after oral fluphenzaine. Thus in a group of 33 patients randomly assigned to receive 5 mg, 10 mg or 25 mg oral fluphenazine daily, steady state plasma fluphenzaine levels at each dose were significantly lower that those of fluphenazine sulfoxide or 7-hydroxy-fluphenazine, although there were no significant differences between the levels of fluphenazine and fluphenazine N^4-oxide. On the other hand, plasma levels of the parent drug were significantly higher than those of any metabolite in a corresponding group of patients at steady state on depot medication. These observations underscore the importance of route dependent differences in the pharmacokinetics of fluphenazine which can lead to problems when switching patients from oral to depot neuroleptics.

The concept of "disabling side-effects" is an important development in understanding relationships between plasma levels of neuroleptic drugs and clinical response in patients with schizophrenia. Risk-benefit analysis shows clearly that evaluation of relationships between plasma levels and clinical response must take into account the consequences of side-effects which the patient feels have a negating effect on therapy. Emerging data on putative therapeutic plasma level ranges in maintenance therapy are potentially important and may be particularly useful in the maintenance of patients on low dose therapy. It is noteworthy that in a carefully executed dose reduction study in treatment resistant patients under medication with haloperidol, the mean lowest effective dose (8.7 ng/mL) lay within the optimal therapeutic range (5 ng/mL to 12 ng/mL) found in acutely psychotic patients. The study showed that gradual dose reduction of neuroleptic was possible in chronic treatment resistant patients with schizophrenia who were originally thought by ward staff to require high doses of neuroleptic. After dosage reduction, the patients experienced fewer side-effects; they were less depressed and hence demonstrated a degree of improvement.

Key Words: pharmacokinetics, clinical pharmacokinetics, fluphenazine, haloperidol, route, oral, depot

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INTRODUCTION

The successful application of pharmacokinetic principles to the posology of neuroleptic drugs in patients with schizophrenia depends on the validity of the concept of "therapeutic ranges" or "therapeutic windows". Moreover, the inclusion of data on key metabolites may also be of value, especially where metabolites contribute to therapeutic activity or toxicity. Even "inactive" metabolites may be important if they sequester a significant fraction of the administered dose and thereby contribute to a problem with bioavailability of active principle(s). Clinicians may not always realize that there are substantial quantitative differences in metabolic profiles of the same neuroleptic when administered by different routes. Thus the extent of contribution of metabolite(s) to therapeutic efficacy and/or toxicity will also be dependent on the route of administration of the parent drug.

In this paper, we shall review some of our work on: 1. effects of route of adminstration on the pharmacokinetics of fluphenazine (FPZ) and some of its metabolites; 2. the clinical pharmacokinetics of fluphenazine in acute patients medicated with oral fluphenazine; 3. the clinical pharmacokinetics of haloperidol in acute patients medicated with oral haloperidol; 4. the clinical pharmacokinetics of fluphenazine in the maintenance of individuals with chronic schizophrenia fluphenazine decanoate; 5. a systematic dose reduction study in maintenance treatment refractory patients with oral haloperidol.

Effects of route of administration on the clinical pharmacokinetics of fluphenazine and some of its metabolites

It is well established that a drug taken orally is subject to metabolism during passage through the gut wall, liver and lungs before reaching the systemic circulation. However, a drug administered by intramuscular injection reaches the systemic circulation without having to undergo this "first pass" metabolism. Thus the route of administration has an important impact on the metabolism and clinical pharmacokinetics of the drug.

We conducted a study in a group of eight DSM-III-R individuals with schizophrenia who had not taken oral neuroleptics for at least two weeks or who had not taken depot neuroleptics for at least three months (Marder et al 1989). The patients were randomly assigned to receive, at bed time, daily oral doses of 5 mg, 10 mg or 20 mg fluphenazine. After 14 days of oral treatment, blood samples were drawn approximately 12 hours after the previous evening dose.

When the clinical condition of the patients had stabilized in response to oral medication, the patients were randomly assigned to receive biweekly 5 mg or 25 mg fluphenazine decanoate. The dose of oral medication was tapered and withdrawn gradually during the first weeks of depot therapy. Blood samples for trough levels (C_{min}) were drawn after the patients had been receiving the same dose of fluphenazine decanoate for at least three months. Plasma levels of fluphenazine (Midha et al 1980) and fluphenazine sulfoxide (Midha et al 1988d) were measured by radioimmunoassays (RIAs).

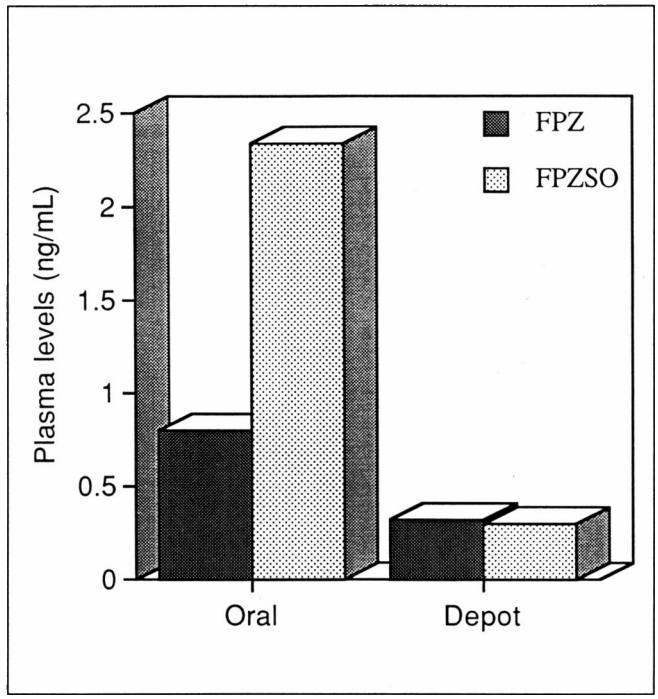


Fig. 1. Mean steady state plasma concentrations of fluphenazine (FPZ) and fluphenazine sulfoxide (FPZSO) in eight patients with schizophrenia who were initially stabilized on oral FPZ and then switched to depot FPZ decanoate.

The results (see Figure 1) showed that mean fluphenazine sulfoxide (FPZSO) plasma levels were threefold greater than those of fluphenazine when the patients were on oral fluphenazine ($t = 7.74$, $p < 0.002$). There was no significant difference between the plasma levels of fluphenazine and its sulfoxide, however, after the same patients had been brought to steady state with depot fluphenazine (Marder et al 1989). The high levels of sulfoxide after oral fluphenazine were largely attributed to "first pass" metabolism, which was circumvented when the drug was given intramuscularly.

After three months on depot drug, mean plasma fluphenazine levels were less than half those previously observed when the patients were on oral drug. This observation arose partly because the biweekly molar doses of depot fluphenazine were lower than the molar doses administered during a corresponding period when the patients were on oral medication. Equally important, however, was the effect of "first pass" metabolism in reducing the bioavailability of parent fluphenazine after oral administration.

In a second study, plasma levels of fluphenazine and its sulfoxide, 7-hydroxy (7-HOFPZ) and N^4-oxide (FPZNO)

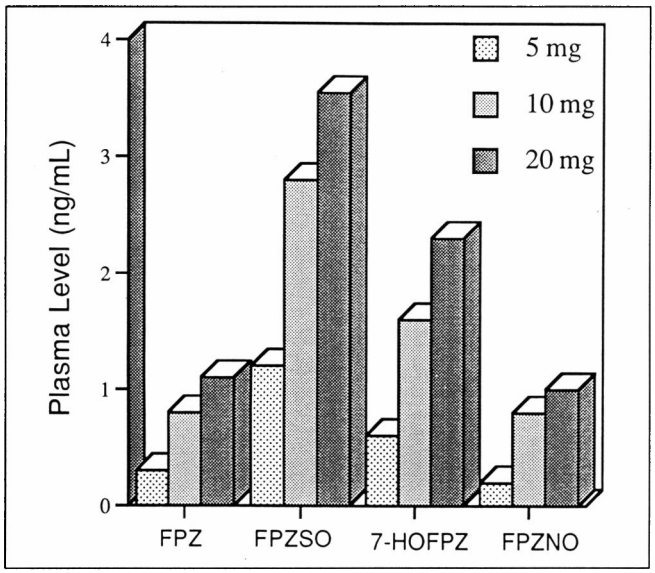


Fig. 2. Mean plasma concentrations of fluphenazine (FPZ), FPZ sulfoxide (FPZSO), 7-hydroxy-FPZ (7-HOFPZ) and FPZ N^4-oxide (FPZNO) in 33 patients receiving 5 mg, 10 mg or 25 mg oral fluphenazine daily for two weeks.

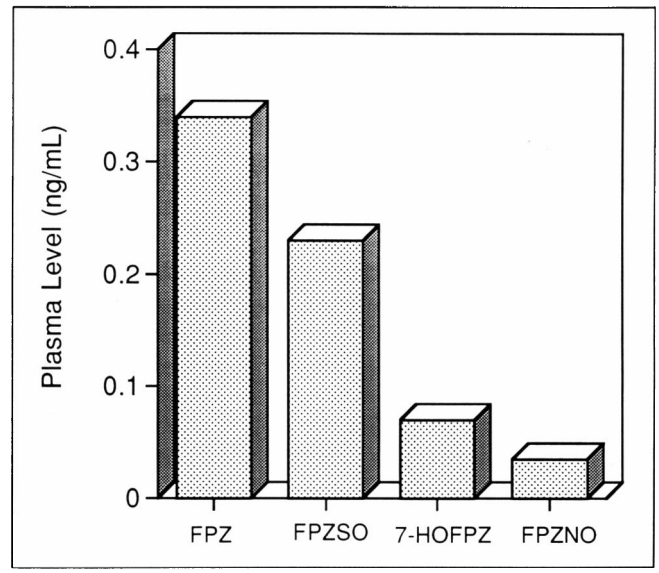


Fig. 3. Plasma concentrations of fluphenazine (FPZ), FPZ sulfoxide (FPZSO), 7-hydroxy-FPZ (7-HOFPZ) and FPZ N^4-oxide (FPZNO) in 23 outpatients with schizophrenia receiving 5 mg FPZ decanoate biweekly for three months.

metabolites were monitored in 33 DSM-III-R individuals with schizophrenia randomly assigned to receive 5 mg, 10 mg or 20 mg oral fluphenazine. Highly sensitive RIAs were employed in the quantitation of fluphenazine (Midha et al 1980; Aravagiri et al 1992) and its sulfoxide (Midha et al 1988d), N^4-oxide (Aravagiri et al 1990) and 7-hydroxy (Aravagiri et al 1993) metabolites in plasma.

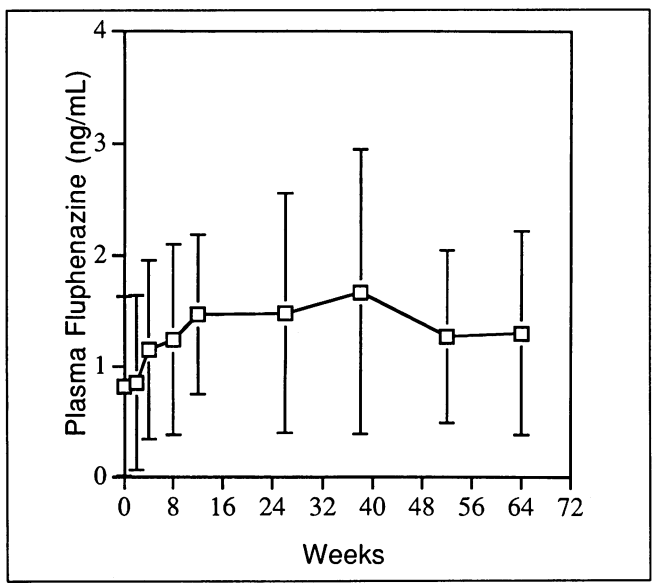


Fig. 4. Mean trough plasma fluphenazine concentrations in 28 patients with schizophrenia receiving 25 mg fluphenazine decanoate through 64 weeks.

At each dose, steady state plasma fluphenazine levels (see Figure 2) were significantly lower that those of the sulfoxide (5 mg, $p = 0.04$; 10 mg $p = 0.001$; 20 mg $p = 0.0001$) or 7-hydroxy metabolites (5 mg $p = 0.04$; 10 mg, $p = 0.09$; 20 mg $p = 0.02$). There were, however, no significant differences between the levels of fluphenazine and fluphenazine N^4-oxide at any dosage level.

All three metabolites clearly play a significant role in the disposition of oral fluphenazine. In order to establish the contribution of these metabolites to the disposition of fluphenazine after intramuscular administration of the decanoate, a study was carried out in which steady state plasma levels of fluphenazine and its sulfoxide, 7-hydroxy and N^4-oxide metabolites were monitored in 23 DSM-III-R individuals with schizophrenia receiving biweekly injections of 25 mg fluphenazine decanoate.

Figure 3 shows that steady state trough (C_{min}) plasma levels of fluphenazine were significantly higher than plasma levels of any of the metabolites. Thus the role of the metabolites in the disposition of fluphenazine is clearly less marked after intramuscular administration such that there are quantitative differences in metabolic profiles between two routes of administration of the same drug.

Generally, in the clinical setting, patients in acute psychosis are "titrated" with oral medication to bring them under therapeutic control. Once stabilized, they may be switched to depot medication for maintenance therapy. Depot medications containing highly lipophilic drug (or prodrug) dissolved in oil are designed to provide sustained plasma levels over long periods of time in order to overcome problems with poor compliance. However, when switching patients from oral to

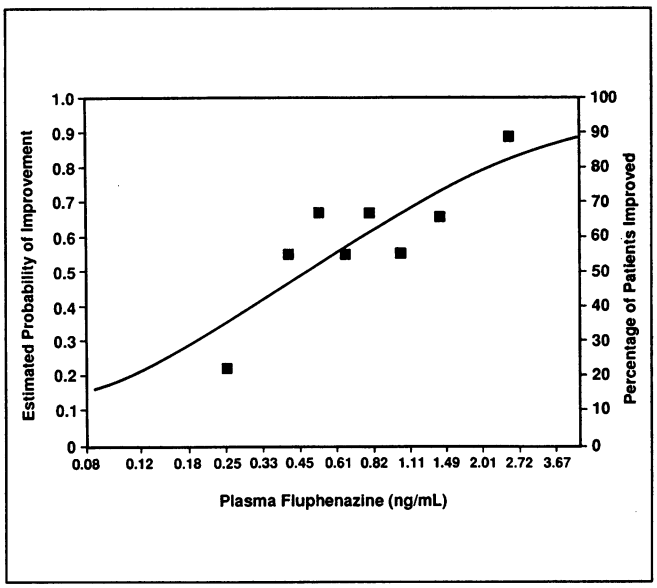


Fig. 5. **Improvement as a function of plasma fluphenazine levels. Each datum point represents the percentage of a subgroup of patients improved (right y-axis) plotted against the mean plasma fluphenazine concentration of the patients in the subgroup. The line represents logistic regression functions (p = 0.0154) which show the relationship between plasma levels of fluphenazine and the estimated probability of improvement (left y-axis).**

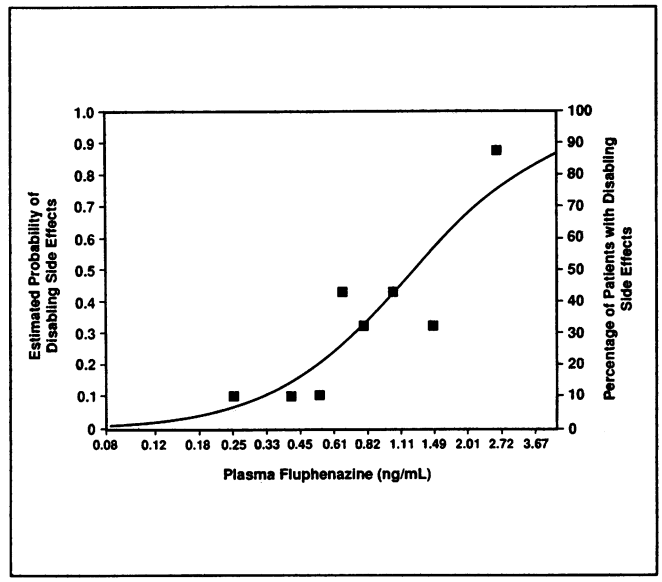


Fig. 6. **Disabling side-effects as a function of plasma fluphenazine levels. Each datum point represents the percentage of a subgroup of patients improved (right y-axis) plotted against the mean plasma fluphenazine concentration of the patients in the subgroup. The line represents logistic regression functions (p = 0.0008) which show the relationship between plasma levels of fluphenazine and the estimated probability of disabling side-effects (left y-axis).**

depot medication, it is important to recognise that it can take several months for the neuroleptic plasma levels to reach the new steady state, leaving the patient vulnerable to exacerbation and relapse. Moreover, the selection of an appropriate dose of depot neuroleptic is difficult because it is impossible to "titrate" a stabilized patient.

The lengthy approach to steady state can be illustrated by a study we carried out in 28 male patients with schizophrenia (DSM-III-R) who received 25 mg biweekly fluphenazine decanoate (Marder et al 1991). Trough plasma levels of fluphenazine over 64 weeks were measured by validated RIA method (Midha et al 1987b).

The plasma level *versus* time profile for the patients on the 25 mg dose is illustrated in figure 4. The time to steady state was calculated by fitting to a segmented nonlinear model (iterative curve fitting procedure). The quadratic function in the early stage before steady state was then joined to a horizontal line (plateau). The time at which these two segments met represented the time to steady state which was calculated to be 11.4 weeks. In other words, it took about three months for plasma fluphenazine levels to reach steady state after patients were switched to medication with fluphenazine decanoate. This observation underscores the importance of oral supplementation during the first three months of treatment with fluphenazine decanoate to safeguard against low plasma levels (Marder et al 1991). It is also advisable to monitor plasma fluphenazine levels during the transition period.

The clinical pharmacokinetics of fluphenazine in acute patients medicated with oral fluphenazine

It is well established that there is wide between-subject variability in plasma levels, even after the administration of the same dose of the same phenothiazine (Midha et al 1988b, 1988c, 1989b; Chakraborty et al 1989) or butyrophenone (Midha et al 1989a) type antipsychotic. There is also a great deal of between-patient variability in responsiveness to both therapeutic effects and side-effects of neuroleptic treatment, even when controlled for plasma concentration. In evaluating therapeutic effectiveness, the impact of potentially incapacitating side-effects on clinical progress and quality of life must be considered. Moreover, the statistical approach to data treatment must be able to cope with a multiplicity of variables.

Techniques which can be employed under these circumstances are logistic regression (Neter et al 1974) and survival analysis with drug or metabolite levels as a covariate. Logistic regression is concerned with the presence or absence of symptoms at any time within the study period, whereas

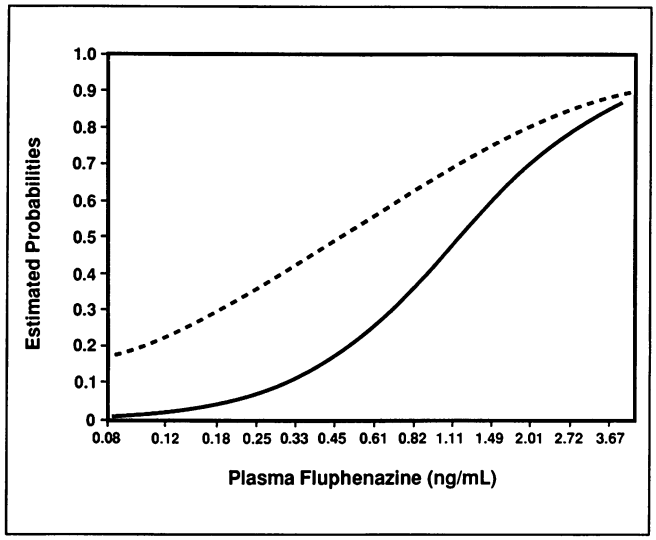


Fig. 7. Relationships between plasma fluphenazine concentrations and estimated probabilities of improvement (broken line) and disabling side-effects (continuous line).

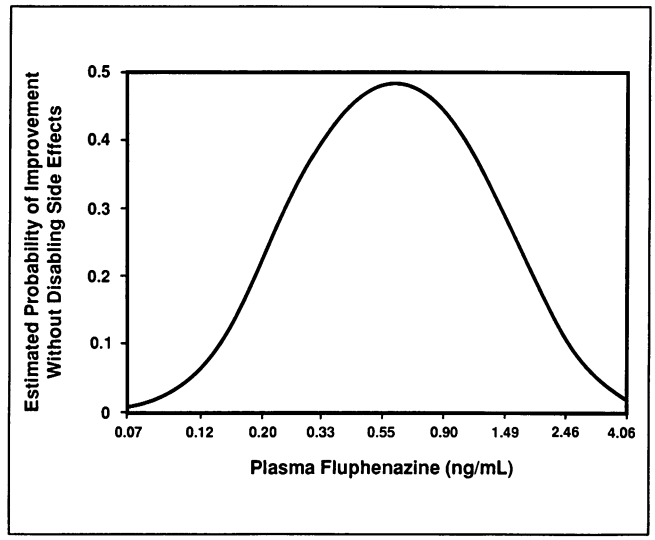


Fig. 8. A "risk-benefit" probability curve obtained by combining the two logistic regression functions shown in Figure 7.

survival analysis is also sensitive to the time of occurrence of symptoms.

A study on oral fluphenazine (Van Putten et al 1991a) was carried out in 72 newly readmitted drug free men suffering from shizophrenia who were randomly assigned 5 mg, 10 mg or 20 mg fluphenazine hydrochloride daily for four weeks. Patients with a history of nonresponse to neuroleptic drugs were excluded, as were those with a history of intractable extrapyramidal side-effects (EPS) with high potency neuroleptics. Plasma levels of FPZ, FPZSO, 7-HOFPZ and FPZNO were measured by RIAs (Midha et al 1993).

The data were analyzed by logistic regression using log plasma levels of drug (or metabolite) as the independent variable with Global Improvement (see Figure 5) and CGI Disabling Side-Effects (see Figure 6) as outcome measures.

Table 1

Correlation matrix of plasma levels of fluphenazine (FPZ) and fluphenazine $N^{4'}$-oxide (FPZNO) and side-effects in 46 patients with schizophrenia

	Disabling side-effects	Akinesia	Akathisia	Akinesia and Akathisia
Mean log FPZ				
r	0.41	0.21	0.30	0.33
p	0.0001	0.06	0.007	0.002
n	86	85	83	85
Mean log FPZNO				
r	0.50	0.50	0.44	0.60
p	0.0005	0.003	0.003	0.0001
n	44	46	45	46

For the purpose of data analysis, disabling side-effects were defined as "side-effects that either interfered with the patient's functioning," or outweighed therapeutic effects as measured by the Clinical Global Impression (CGI) scale. In Figure 5, the data points were computed by ranking the plasma levels from lowest to highest. The data were then divided into eight equal subgroups. The percentage of improved patients was computed for each subgroup, and the data point placed at the midpoint of the plasma range for each subgroup. The line in Figure 5 represents logistic regression functions calculated from the data. It shows the relationship between plasma levels of fluphenazine and the estimated probability of improvement.

In Figure 6 the data points were computed similarly to Figure 5 by ranking the plasma levels from lowest to highest. The percentage of patients with disabling side-effects was computed for each subgroup and the data point placed at the midpoint of the plasma level range for each subgroup. The line represents logistic regression functions calculated from the data. It shows the relationship between plasma levels of fluphenazine and the estimated probability of disabling side-effects.

Many patients who complained of disabling side-effects did not objectively appear to be over-medicated or distressed by side-effects. From the patients point of view, however, the therapeutic index of fluphenazine is much narrower than is generally supposed. Moreover, the subjective descriptions of the patients are reflected in the probability curve

Table 2

Improvement in BPRS Psychosis Factor in four plasma haloperidol ranges

	Ineffective	Threshold	Optimal	Toxic
	n = 12	n = 14	n = 30	n = 13
Plasma Level Range (ng/ml)	< 2	2-5	5.1 - 12	> 12
Mean ± SD improvement in BPRS-Psychosis factor	2.4 ±4.9	4.2 ±4.4	8.8 ±5.0[a]	4.6 ±3.7

[a] improvement better than that at threshold or toxic levels p = 0.004

in Figure 6. The combination of the two probability curves (Figures 5 and 6) into a single plot (Figure 7) illustrates the phenomenon much more clearly. At the higher plasma fluphenazine levels, there is a high probability of improvement but there is also a high probability of disabling side-effects. For example, in the subgroup of patients with the highest plasma fluphenazine levels (mean 2.7 ng/mL), 90% showed improvement but 90% also showed disabling side-effects.

The "risk-benefit curve" (see Figure 8) was derived by a combination of the two logistic regression functions in Figure 7 to give a single probability curve. It is important to recognize that the risk-benefit curve is *not* a dose response curve. It shows the relationship between plasma levels of the drug and the probability of improvement without disabling side-effects. For example, at a plasma fluphenazine level of 0.67 ng/mL, there is a maximum probability (0.48) of improvement without disabling side-effects. Above 0.67 ng/mL, an increasing number of patients improve with respect to their psychotic symptoms but with a progressive increase in disabling side-effects. Thus it appears that the risk-benefit analysis is the most appropriate approach to the evaluation of data on neuroleptic plasma levels and clinical response.

Analysis of data from the 37 randomized cases (Van Putten et al 1991a) suggested that the N^4-oxide metabolite was more strongly associated with disabling side-effects than was the parent fluphenazine. The relationships were strengthened when analysis included data from nine other patients who were not randomized but assigned to the 5 mg or 10 mg dose because of a history of severe EPS (see Table 1).

These data suggest that fluphenazine N^4-oxide may be associated with side-effects. No significant relationships were found between plasma levels of the sulfoxide or 7-hydroxy metabolite and disabling side-effects.

The clinical pharmacokinetics of haloperidol in acute patients medicated with oral haloperidol

A similar study of oral haloperidol (Van Putten et al 1992) was carried out in 69 newly readmitted drug free men with schizophrenia who were randomly assigned to receive 5 mg, 10 mg or 20 mg haloperidol daily for four weeks. Unlike the oral fluphenazine study (Van Putten et al 1991a), however, haloperidol nonresponders were not excluded. Rather, in cases of nonresponse after the first four weeks of fixed dose treatment, the dose of haloperidol could be adjusted by clinical impression for a further period of four weeks. Clinical status was assessed in semi-structured interviews using the Brief Psychiatric Rating Scale (BPRS) and the Clinical Global Impression scales. Clinical response was measured at baseline, weekly

Table 3

Effect of reducing plasma haloperidol levels < 12 ng/mL on BPRS subscales (change scores relative to baseline n = 8)

	Haloperidol ng/mL ± SD	BPRS-S	BPRS-D	BPRS-P	BPRS-R
Weeks 1-4	15.0 ± 2.1	5.1 ± 1.6	1.0 ± 4.3	2.4 ± 2.9	-2.3 ± 3.4
Weeks 5-8	7.8 ± 2.1	6.4 ± 2.2	2.8 ± 3.8	3.0 ± 3.5	-0.1 ± 3.8
t-statistic[a]		2.76	—	1.93	5.34
p		< 0.05	—	< 0.10	< 0.01

Ratings on BPRS subscales for Schizophrenia (S), Depression (D), Paranoia (P), and Retardation (R). Higher change scores = improvement; negative scores = deterioration.
[a] Two-tailed paired t-test

Table 4

Effect of increasing plasma haloperidol levels in relative non-responders (change scores relative to baseline n = 8)

	Haloperidol ng/mL ± SD	BPRS-S	BPRS-D	BPRS-P	BPRS-R
Weeks 1-4	7.0 ± 4.0	1.7 ± 2.2	0.3 ± 1.2	1.5 ± 2.3	-1.2 ± 2.7
Weeks 5-8	17.8 ± 5.0	2.7 ± 2.0	-1.0 ± 2.2	-0.03 ± 2.6	-3.8 ± 4.1
t-statistic[a]					2.33
p		NS	NS	NS	< 0.01

Ratings on BPRS subscales for Schizophrenia (S), Depression (D), Paranoia (P), and Retardation (R). Higher change scores = improvement; negative scores = deterioration.
[a] Two-tailed paired t-test

Table 5

Global improvement at the end of the fixed dose period with haloperidol (n = 68)

	Plasma Haloperidol (ng/mL)			
	Range	Mean ± SD	Improved[a]	% Improved
Ineffective	< 2	1.3 ± 0.5	1 out of 11	9
Threshold	2 - 5	3.2 ± 0.7	6 out of 14	43
Optimal	5 - 12	8.2 ± 1.6	22 out of 30	73
Toxic	> 12	15.2 ± 2.7	5 out of 13	39

$x^2 = 10.75$; df = 3; p = 0.013

[a]Improved = very much improved or much improved on the CGI scale

Table 6

Plasma fluphenazine levels as predictors of psychotic exacerbation during the following year

	Survival Analysis (Cox Models)		Logistic Regression	
Week	x^2	p	x^2	p
12	0.87	0.35	0.21	0.65
26	3.77	0.052	4.38	0.04
38	12.21	0.0005	8.98	0.003

for the first four weeks and at week eight after the flexible dose period.

The results (see Table 2) suggested an optimal plasma level range of 5 ng/mL to 12 ng/mL of haloperidol. At plasma levels higher than 12 ng/mL, the presence of unpleasant side-effects tended to negate the therapeutic benefit of haloperidol.

In order to test the validity of the proposed therapeutic range, the dose of haloperidol was reduced in eight patients with plasma levels > 12 ng/mL in order to bring the plasma levels closer to the proposed optimal therapeutic range. After plasma levels had decreased to an average of 7.8 ng/mL in response to dose reduction, the patients experienced fewer side-effects and were less psychotic, less dysphoric and less retarded. In no case was deterioration observed (see Table 3).

In six patients with plasma levels below the proposed therapeutic range (1.42 0.28 ng/mL), the dose of haloperidol was increased in an attempt to bring the plasma levels closer to the therapeutic range. Again, all patients improved (Clinical Global Impression) as their plasma levels were raised (3.1 1.8 ng/mL) and brought into the "threshold range" (2 ng/mL to 5 ng/mL). However, two patients with initial plasma levels of 1.4 ng/mL and 1.9 ng/mL did not subsequently improve at any plasma level, indicating that they were nonresponders to haloperidol. Similarly, in eight other nonresponders, the plasma levels were raised to above 12 ng/mL by increasing the dosage of haloperidol. When in the higher range (mean 17.8 ng/mL), 6/8 patients became worse on the global improvement ratings, and they were more dysphoric.

Global improvement was evaluated at the end of the fixed dose period in all 68 patients who completed the study. Table 5 demonstrates that maximum percent improvement was observed in the optimal range (5 ng/mL to 12 ng/mL) of haloperidol plasma levels.

Note that the sum of all patients showing improvement (n = 34) regardless of plasma level ranges is exactly 50% of the number of patients who completed the study (n = 68), a result which has been observed (Midha et al 1987a) in a number of fixed dose studies of this type which do not exclude nonresponders.

Risk-benefit analysis showed that at a plasma level of 12 ng/mL haloperidol, the probability of disabling side-effects (Van Putten et al 1991b) is approximately 0.65 (see Figure 9). As the plasma level increases, so does the probability of disabling side-effects. The clinician must seek the appropriate balance between disabling side- effects and improvement.

The clinical pharmacokinetics of fluphenazine in the maintenance of chronic cases of individuals with schizophrenia with fluphenazine decanoate

Much of the research on therapeutic ranges has been carried out in patients in the acute phase of schizophrenia. There are relatively few data on therapeutic ranges for neuroleptics in maintenance therapy of the chronic phase of the disorder, although such data would clearly be of value

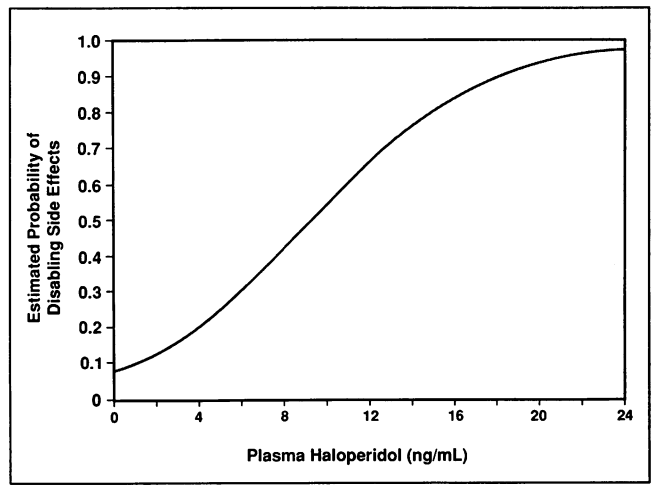
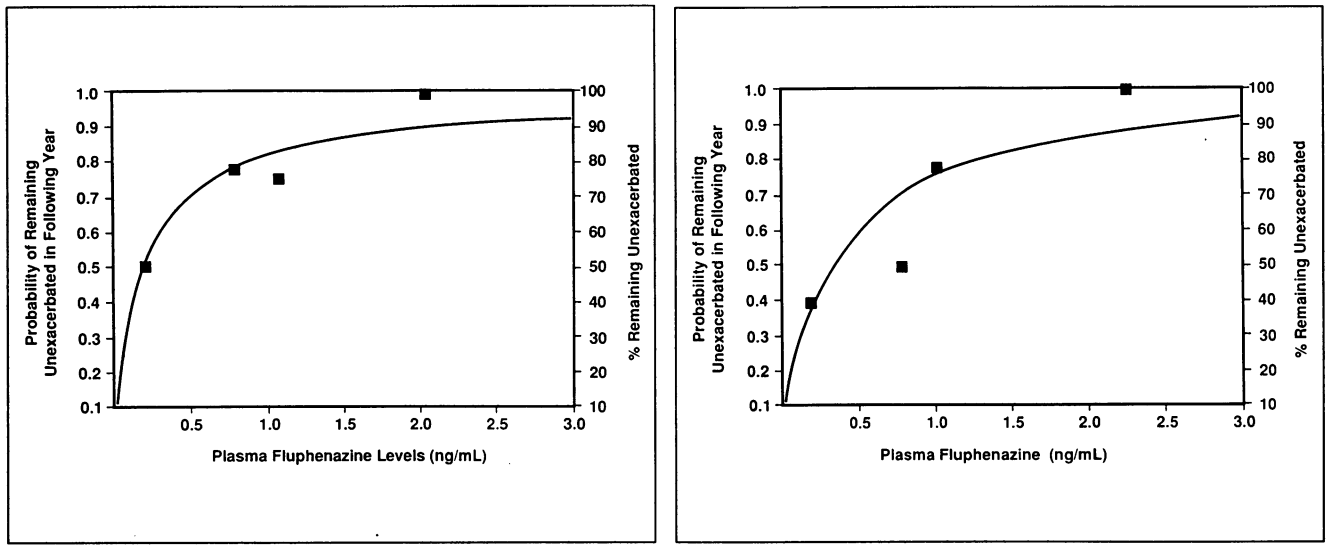


Fig. 9. The relationship between plasma haloperidol and the estimated probability of disabling side-effects [Logistic regression function (p = 0.0002)]



10a. 10b.

Fig. 10. Plasma fluphenazine level at six months (see Figure 10a) or nine months (see Figure 10b) as a predictor of unexacerbation in the following year. Each datum point represents the percentages of a subgroup of patients remaining unexacerbated during the following year (right y-axis) plotted against the mean plasma fluphenazine concentration of the patients in the subgroup. The line represents logistic regression functions (Figure 10a, p = 0.052; Figure 10b, p = 0.0005) which show the relationship between plasma levels of fluphenazine and the estimated probability of remaining unexacerbated in the following year (left y-axis).

the disorder, although such data would clearly be of value because it is impossible to "titrate" dose against response in stabilized patients.

In a double blind comparison of 5 mg or 25 mg fluphenazine decanoate, we examined relationships between plasma fluphenazine levels at three, six and nine months and psychotic exacerbations during the following year (Marder et al 1990). The data were analyzed by logistic regression and survival analysis with log fluphenazine levels as a covariate (Cox Models). The log transform was carried out in order to normalize the distribution of plasma concentrations.

Logistic regression (see Table 6) indicated that the relationship between log plasma levels and psychotic exacerbation the following year was significant at 26 and 38 weeks but not at 12 weeks. Examination of the data by survival analysis gave similar results. The relationship between log plasma levels and psychotic exacerbation the following year was significant at 26 and 38 weeks but not at 12 weeks.

These data are illustrated graphically in Figures 10a and 10b. The data points were computed by ranking the plasma levels from lowest to highest. For each quartile of the sample, the percentage remaining unexacerbated the following year was computed and the datum point placed at the midpoint of the plasma range for each quartile. In each plot, the line represents logistic regression functions calculated from the data. It shows the relationship between plasma levels and the probability of relapse during the following year.

Figures 10a and 10b indicate that patients with relatively low plasma levels (for example, less than 0.5 ng/mL) had a substantially poorer rate of survival during the following year than those with levels above 1.0 ng/mL. Those patients with higher tolerance for fluphenazine would have relatively lower risk for relapse if their plasma levels were maintained at about 1.0 ng/mL. Hence, plasma level monitoring may be especially useful in patients maintained with low doses of fluphenazine decanoate.

A systematic dose reduction study in maintenance treatment refractory patients with oral haloperidol

In a manuscript entitled *A systematic approach to treatment resistance in schizophrenic disorders* by May et al (May et al 1988) it was stated that "treatment resistance in schizophrenic disorders is a major mental health problem. It is seldom, if ever, resistance to drug treatment alone, but must be understood in the context of interactions between drug and non-drug treatment, and in the nature and source of the resistance." It has been our observation that many treatment resistant patients are given very high doses of neuroleptic medication even though by definition they are incapable of responding fully to conventional neuroleptics. It occurred to us, therefore, to test the hypothesis that a significant number of such patients might actually benefit from a reduction in the dose of neuroleptics in terms of diminution of side effects and improvements in quality of life. If the hypothesis proved

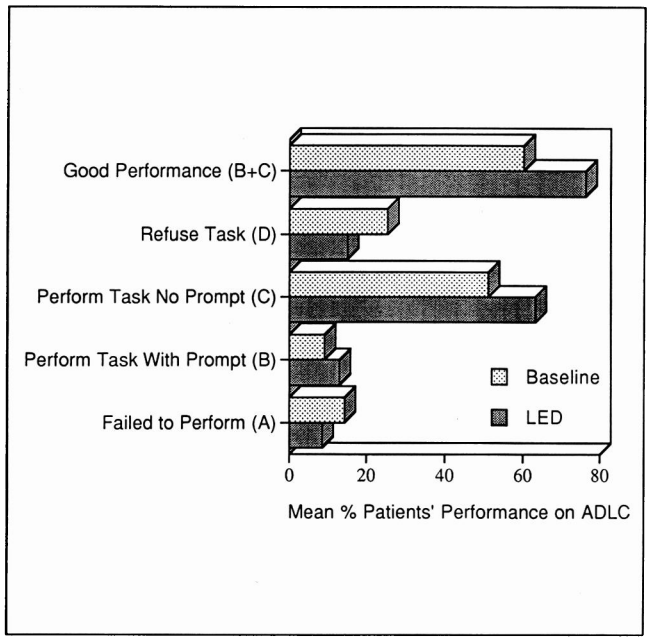


Fig. 11. Mean percentage performance of patients on the Activities of Daily Living Checklist at baseline and at the lowest effective dose (LED).

to be correct, an important spin off might be manifested as a lowered requirement for costly in-hospital supervision.

A dose reduction study was carried out in 13 chronic treatment resistant (TR) individuals with schizophrenia (DSM-III-R). The patients were all institutionalized with at least two years of persistently high psychotic symptoms and no prospect of release after at least six months of continuous treatment. Each patient had received extensive treatment with various neuroleptics for at least three months at a chlorpromazine equivalent dose of 1000 mg/day or higher. In other words, the patients were all severely treatment resistant at level six of the scale proposed by May et al (May et al 1988). There was no history of alcoholism, drug addiction or evidence of seizure disorders or organic brain syndrome. However, nine of the 13 patients had a history of assaultiveness.

At the start of the study, each patient was receiving at least 50 mg haloperidol per day. The patients were maintained at their usual high dose of haloperidol (without adjunctive drugs) for two months for baseline evaluation (an extensive battery of tests including CGI, the BPRS, the MACC Behavioral Adjustment Scale, the Idiosyncratic Target Symptoms Scale (ITSS), The Activities of Daily Living Checklist (ADLC) and the Barnes Akathisia Scale (BAS). The dose of haloperidol was reduced (as tolerated) every five weeks according to a fixed schedule: 65-50-35-20-15-10-5-0 mg/day (one week was allowed for haloperidol to reach the new steady state and four weeks of maintenance was allowed for clinical evaluation as above).

Dosage reduction was determined by a consensual interdisciplinary team using the CGI as follows. If the CGI rating was six (much worse) or seven (very much worse), dosage reduction was concluded and the dose was returned to the lowest previous effective dose (LED). A rating of five (minimally worse) resulted in another five weeks at the same dose. If no further worsening occurred, dosage reduction was resumed. A rating of four (no change) qualified the patient for reduction to the next target level. The study was completed when all patients had been brought to LED.

The drug was administered at bed time as liquid concentrate diluted to 50 mL with water and given with either fruit juice or Kool Aid to disguise taste. Blood samples were drawn ten to 12 hours after the previous dose. Plasma levels of haloperidol and reduced haloperidol were analyzed by HPLC (Midha et al 1988a).

On average, the 11 patients who tolerated dose reduction improved on the BPRS total score (mean change +5.9; $p = 0.06$) and the BPRS Depression Factor (mean change +0.55; $p = 0.06$). On the CGI Severity Index, there was no significant change (5.1 *versus* 4.8) and the average CGI Global Improvement Index in these patients was 3.85 ± 0.67 (3 = minimally improved and 4 = no change). Moreover, at the LED, the patients experienced fewer side-effects, less akathisia on the BAS (total score 2.1 *versus* 1.2, $t = -1.99$, $df = 10$, $p = 0.04$, one tailed), and less EPS on the Unified Parkinson's Disease Rating Scale (total score 13.2 *versus* 5.8, $t = 2.64$, $df = 10$, $p = 0.01$, one tailed).

There were no significant changes in behavioral measures such as the MACC and the ITSS despite the mean dosage reduction from 61.8 ± 12.5 mg/day to 17.3 ± 10.3 mg/day in the treatment resistant patients. After the dose reduction, the patients tended to be less negativistic. For example, on the ADLC, patients' "refusal to perform tasks" decreased at the LED, as shown in Figure 11.

An increase in violent behavior ($p = 0.02$) during the dose reduction period was observed in these patients. Upon elimination of the data of patients four and ten, who could not tolerate dose reduction because of an increase in violent behavior, the remaining patients still showed a modest increase in violence during the dosage reduction ($p = 0.08$). However, once the patients were restabilized at the LED, there were no significant differences (signed rank test) in violent incidents compared to baseline.

The dose reduction study showed that gradual dose reduction of neuroleptic was possible in chronic treatment resistant patients with schizophrenia who were originally thought by ward staff to require high doses of neuroleptic. After dosage reduction, the patients experienced fewer side-effects; they were less depressed and hence demonstrated a degree of improvement. There was also a modest increase in violent behavior during the dose reduction period which did not persist after stabilization at the LED. The 72% reduction in dose resulted in a 77% reduction in plasma levels of haloperidol at the LED.

the optimal therapeutic range (5 ng/mL to 12 ng/mL) proposed by Van Putten et al (Van Putten et al 1992) for acutely psychotic patients. At the LED, the corresponding reduction in the plasma levels of reduced haloperidol was 90%. The significance of reduced haloperidol plasma levels remains to be clarified, although it has been suggested that patients with relatively high levels of reduced haloperidol tend to be less responsive to therapy with haloperidol than those with lower levels of the metabolite (Altamura et al 1987).

CONCLUSIONS

We believe that the concept of "disabling side-effects" is an important development in understanding relationships between plasma levels of neuroleptic drugs and clinical response in patients with schizophrenia.

Emerging data on putative therapeutic plasma level ranges in maintenance therapy are potentially important and may be particularly useful in the maintenance of patients on low dose therapy. It is noteworthy that in the carefully executed dose reduction study in treatment resistant patients under medication with haloperidol, the mean lowest effective dose (8.7 ng/mL) lay within the optimal therapeutic range (5 ng/mL to 12 ng/mL) found in acutely psychotic patients.

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